Platelet Dysfunction Associated With Insulin Therapy in Patients With Type 2 Diabetes: Please Do Not Throw the Baby Out With the Bathwater!

We read with interest the study by Angiolillo et al. (1) demonstrating that patients with type 2 diabetes have increased platelet aggregation on dual aspirin–clopidogrel therapy and that patients with insulin-treated diabetes mellitus (ITDM) have greater adenosine diphosphate (ADP)-induced platelet aggregation compared with patients with non–insulin-treated diabetes mellitus (NITDM) (1). This is an important observation as 42% of 15,603 randomized patients (in the CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trial) had diabetes (17% treated with insulin), with no significant better cardiovascular protection of the clopidogrel plus aspirin combination versus aspirin alone (2). However, Angiolillo et al.'s (1) finding and interpretation might be considered by cardiologists as a counterproductive effect of insulin therapy and represent an erroneous argument for not switching to insulin those numerous type 2 diabetic patients with poor glucose control while on oral treatment.

Type 2 diabetes is a progressive disease. Even if it is true that patients with ITDM are at a more advanced stage of their metabolic disorder, the need to switch to insulin reflects profound insulin secretory defect rather than more severe insulin resistance (3,4), as erroneously stated by Angiolillo et al. (1). That the higher proportion of women among ITDM subjects may be considered as an argument supporting the insulin-resistance hypothesis should also be challenged, as greater insulin resistance in women than in men is not a classical finding if appropriately measured (5).

Besides glucose-lowering therapy, the most important clinically relevant difference between the 2 groups was the 1% difference in hemoglobin A_{1c} (HbA_{1c}) level (7.9% in ITDM patients vs. 6.9% in those with NITDM, $p < 0.001$), that is, the same difference as that reported in the intensive group versus the conventional group in the United Kingdom Prospective Diabetes Study (6). Angiolillo et al. (1) suggested that this 1% difference could not explain the difference in platelet reactivity as HbA_{1c} levels were not correlated with any of the platelet-function assays performed. This finding is in contrast to other observations showing a significant influence of glucose levels on platelet reactivity and effect of antiplatelet agents (7). According to Angiolillo et al. (1), the study was conducted in a tightly controlled diabetic population, which led to a limited variability in HbA_{1c} levels; however, the reported 6% coefficient of variation of HbA_{1c} levels looks astonishingly low with regard to the mean ± SD data of the 2 subgroups (7.9 ± 1.5% vs. 6.9 ± 1.0%).

A key message from the study by Angiolillo et al. (1) is that aggressive and/or tailored antithrombotic regimens for high-risk patients such as diabetic patients may be warranted. However, emphasizing in the "therapeutic implications" section that "treatment with insulin is typically considered a surrogate of increased atherothrombotic risk" may be misleading. Although this remains a controversial issue, numerous data do not support this statement (8). As diabetologists, the key objective is to obtain adequate metabolic control (HbA_{1c} <7% and ideally <6.0%), in combination with aggressive management of all other cardiovascular risk factors, including effective antiplatelet therapy (9). In numerous patients, insulin therapy is a necessary and often irreplaceable partner to tackle hyperglycemia and reach HbA_{1c} targets. Please do not throw the baby out with the bathwater!

***André J. Scheen, MD, PhD**
Delphine Legrand, MD

*CHU Liège
Division of Diabetes, Nutrition, and Metabolic Disorders
Department of Medicine
CHU Sart Tilman
University of Liège
Liège 4000
Belgium
E-mail: andre.scheen@chu.ulg.ac.be

doi:10.1016/j.jacc.2006.11.004

REFERENCES

1. Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006; 48:298–304.
2. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17.
3. Scheen AJ, Lefèbvre PJ. Insulin resistance vs. insulin deficiency: which comes first? The old question revisited. In: Di Mario U, Leonetti F, Pugliese G, Sbraccia P, Signore A, editors. Diabetes in the New Millennium. New York, NY: Wiley, 2000:101–13.
4. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003;46:3–19.
5. Ferrannini E, Natali A, Bell P, et al. Insulin resistance and insulin secretion in obesity. J Clin Invest 1997;100:1166–73.
6. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
7. Watala C, Boncler M, Gresner P. Blood platelet abnormalities and pharmacological modulation of platelet reactivity in patients with diabetes mellitus. Pharmacol Rep 2005;57 Suppl:42–58.
8. Muis MJ, Bots ML, Grobbee DE, Stolk RP. Insulin treatment and cardiovascular disease: friend or foe? A point of view. Diabet Med 2005;22:118–26.
9. American Diabetes Association. Standards of medical care in diabetes mellitus—2006. Diabetes Care 2006;29 Suppl 1:S4–S42.

Reply

We appreciate the comments raised by Drs. Scheen and Legrand. In their letter, they reveal a status of "apprehension" toward the potential impact of our study (1) on how clinicians may approach glucose-control management, in particular, avoiding switching to insulin in patients not well controlled on oral glucose-lowering medication. Recognizing the importance of the concerns raised regarding the potential unintended effects of our investigation (1) this was neither the intent nor the correct interpretation of our findings.

Insulin-treated diabetes mellitus (ITDM) patients are at a more advanced stage of their metabolic disorder, which implies biological differences with patients with non-ITDM. In type 2 diabetes mellitus (T2DM), insulin resistance is a pivotal component of the metabolic disorder, which increases over time. We agree with Drs. Scheen and Legrand that progression of the disease may include a deficiency in insulin secretion, and consequently may lead patients to require exogenous insulin therapy (2). However, this does not invalidate our findings. In fact, it is well established that patients with a longer history of T2DM—thus at an advanced stage of insulin resistance—are more prone to have less optimal glycemic control on oral medication and to require exogenous insulin therapy. Scheen et al. disagree with our interpretation regarding the prevalence of female subjects in the ITDM group. Although evaluation of this aspect was not within our study objectives, we provide recent and robust literature to explain our study findings.

Drs. Scheen and Legrand also raise concerns regarding the impact of hemoglobin A_{1c} (HbA_{1c}) levels on platelet reactivity. We would like to rectify that in our study, the coefficient of variation of HbA_{1c} levels in our T2DM study population was ~16%, and not 6%, which is still narrow overall (3), especially when compared to the broad variability of platelet-function measures. Although we recognize that glucose control plays a pivotal role on platelet reactivity, no correlation between the two variables was observed in our study. This finding supports the hypothesis that there may be more explicit biological differences between ITDM and non-ITDM. Although our results (1) differ from the findings of Watala et al. (4), profound differences exist between the 2 studies. These differences include number of patients, type of antiplatelet treatment, degree of glycemic control, and platelet-function assays used.

Our study is the largest platelet-function analysis performed in T2DM on sustained dual antiplatelet therapy (1). Most studies assessing platelet function in T2DM do not describe differences between ITDM and non-ITDM or they fail to find any difference due to limited patient sample sizes (5). This can result in failure to appreciate the biological factors contributing to the less favorable prognosis in ITDM and may also explain why many clinicians incorrectly consider insulin treatment per se a "surrogate" of increased atherothrombotic risk. Our study demonstrates that biological differences exist between the subgroups of patients with T2DM. Indeed, we agree with Drs. Scheen and Legrand that the biological effects of insulin remain controversial (6). However, ITDM represents among the highest risk of patients for recurrence of atherothrombotic events.

"Do not throw the baby out with the bathwater"? Indeed, as cardiologists, we also concur that insulin therapy is necessary and often irreplaceable to optimally treat hyperglycemia in T2DM. Nevertheless, this should not hinder our efforts to proactively investigate alternative factors that contribute to the enhanced atherothrombotic risk and that affect T2DM, and it is important that we continue to explore more aggressive and/or customized antithrombotic treatment regimens in these high-risk patients (7).

***Dominick J. Angiolillo, MD, PhD, FACC, FESC**
Esther Bernardo, BSc
Marco A. Costa, MD, PhD, FACC
Manel Sabaté, MD, PhD
Theodore A. Bass, MD, FACC
Carlos Macaya, MD, PhD
Antonio Fernandez-Ortiz, MD, PhD

*Division of Cardiology
University of Florida
Shands Jacksonville
655 West 8th Street
Jacksonville, Florida 32209
E-mail: dominick.angiolillo@jax.ufl.edu

doi:10.1016/j.jacc.2006.11.003

REFERENCES

1. Angiolillo DJ, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006; 48:298–304.
2. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003;46:3–19.
3. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. High clopidogrel loading dose during coronary stenting: effects on drug response and interindividual variability. Eur Heart J 2004;25:1903–10.
4. Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)—its relation to metabolic control. Thromb Res 2004;113:101–13.
5. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. Diabetes 2005;54:2430–5.
6. Muis MJ, Bots ML, Grobbee DE, Stolk RP. Insulin treatment and cardiovascular disease; friend or foe? A point of view. Diabet Med 2005;22:118–26.
7. Alfonso F, Angiolillo DJ. Platelet function assessment to predict outcomes after coronary interventions: hype or hope? J Am Coll Cardiol 2006;48:1751–4.